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EFFECTS OF ATROPINE SULFATE ON AIRCREW PERFORMANCE

A Review and Evaluation

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NOTICES

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This report has been reviewed and is approved for publication.

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The human/animal literature on performance effects of atropine sulfate is reviewed and extrapolated to aircrew requirements. Subjective reports and physiological dose-response curves are used to estimate effective dosage levels for performance; ED50 is the dose at which 50% of an aircrew experiences a detectable performance change. Based on this review and extrapolation, the ED40 level for atropine sulfate is 2 mg IM/person for performance effects on near vision, alertness, equilibrium, response-force discrimination, and enunciation: the ED5 level is estimated at 1.35 mg IM/person. Although the published literature on simultaneously administered acetylcholinesterase inhibitors and blockers is insufficient to warrant even a tentative conclusion, the initial results suggest a combined mode of action in the visual system; if confirmed, such action would limit the use of atropine to counteract chemical-warfare performance decrements. Thus although atropine may be lifesaving, it does not prevent aircrew performance losses due to chemical-warfare agents and may impose additional decrements.

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EFFECTS OF ATROPINE SULFATE ON AIRCREW PERFORMANCE
A Review and Evaluation

Chemical warfare (CW) agents are primarily acetylcholinesterase inhibitors such as sarin and soman. Acetylcholinesterase blockers such as atropine sulfate are antagonistic to the inhibitors, so using atropine sulfate as a CW antidote seems logical. This seemingly logical relationship between these blockers and inhibitors has, in part, led to the proposed use of atropine sulfate in the field (U.S. Army Technical Manual 8-258) and to the procurement of autoinjector kits consisting of three 2-mg atropine sulfate IM units. This situation raises three critical questions: First, is a total treatment of 6 mg atropine sulfate sufficient to save the life of someone exposed to sarin or soman? Second, assuming that the life is protected, can atropine sulfate be used to counteract the antiperformance effects of the inhibitor? And third, can someone who is not threatened by an acetylcholinesterase inhibitor but who injects 2, 4, or 6 mg of atropine sulfate continue to perform effectively in a combat role?

Headley (8) has addressed the third question and, based upon an extensive review of the literature, supports the conclusion that Army field personnel can continue to perform combat roles, albeit diminished, under a low dose of unchallenged atropine sulfate. Although the Headley review is the most thorough and substantial piece of scholarship on this issue, it is based on research reports not oriented to high-technology performance on the modern battlefield. This limitation of research reports becomes more critical as we attempt to interpret literature in terms of aircrew performance, an effort as yet unpublished. As Headley points out, such research has not been done. The purpose of our report is to review the existing research, extrapolate these published results to aircrew environments, and evaluate the role of atropine sulfate in addressing the three critical questions.

ATROPINE DOSE LEVELS, UNCHALLENGED AND CHALLENGED

Atropine Unchallenged

Although the median lethal dose (LD50) of atropine (unchallenged) for humans does not appear in the literature we reviewed, the Registry of Toxic Effects of Chemical Substances (19) reports toxic dose levels in several species: e.g., the least oral-dose level sufficient to produce toxic pulmonary effects in a child is 20 µg/kg. The subcutaneous LD50 is 150 mg/kg in the monkey, 1060 mg/kg in the mouse, and 3000 mg/kg in the rat. The IM LD50 is 995 mg/kg in the rat. The IV LD50 is 41 mg/kg in the rat, 31 mg/kg in the mouse, and 70 mg/kg in the rabbit.

Kaiser and McLain (11) reported on the metabolism of a 2-mg dose of N-methylatropine (unchallenged); they had labeled the drug with carbon-14. Two male and two female subjects, ranging in age from 19 to 39 yr and in weight from 138 to 160 lb (62.6-72.6 kg), were observed for 48 h after dose administration. Peak concentrations of carbon-14 were observed in blood

samples. Peak concentrations of carbon-14 were observed in blood samples approximately 30 min after IM injection. Corresponding peaks were observed 75 min post IM in expired air and 120 min in urine. Concentration levels were highest in urine—100 times greater than carbon-14 in blood concentrations and 5000 times greater than in expired air. Urinary excretion of atropine ranged from 87% to 93% within the first 24 h and 1.5% in the second 24 h; 80% was excreted within 8 h. Thus if an unchallenged 2-mg dose of atropine sulfate were a sufficient condition to ground an aircrew, a minimum of 8 h and maximum of 24 h would be required before the aircrew could return to flying duty.

Atropine Challenged

Dose levels for medical treatment other than organophosphate (OP) poisoning commonly range from 0.4 to 0.6 mg (17) in syringes of 0.1 to 1.2 mg/ml (5). The IV dose effect is seen in 1-4 min, reaching a maximum in 8 min (7). The treatment of choice for OP poisoning is 2-4 mg IV every 5-10 min until symptoms of atropinization appear (7). This rate would quickly exceed the U.S. Army individual field issue, given a low exposure. Furthermore, exposure to anticholinesterase compounds increases the body's tolerance to atropine (6), so even greater dosages might be required. Research on successive challenges (multiple exposures), as would be expected in a protracted war, has not been reported.

Treatment by atropine sulfate for anticholinesterase effects of OP poisoning has a moderately well documented history. Various practitioners report total treatment dosages of 240 mg (27), 433 mg (14), 850 mg (22), and 2620 mg (10). Hopmann and Wanke (9) reported treating OP poisoning with 600 mg/day to a total of 11,442 mg; Warriner et al. (26) administered 1600 mg/day to a total of 3911 mg. In view of this literature, the three 2-mg autoinjectors in the U.S. Army field kit may be an insufficient challenge to the organophosphate-like effects of sarin or soman.

Assuming a greater toxicity for sarin or soman than for organophosphates, the life-saving potential of 6 mg atropine sulfate is questionable. This question is exacerbated by the atropine-tolerance problem and the multiple-exposure problem. The additional effects of sarin and soman on deterioration of the nerve membrane are unaddressed. However, if we assume the organophosphate effects to be a conservative test of the hypothesis, 6 mg of atropine sulfate appears insufficient to sustain unprotected life on a chemical battlefield. Consideration of adverse effects on performance in order to plan the return of exposed aircrew to duty is another question.

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EFFECTS OF UNCHALLENGED ATROPINE ON PERFORMANCE

An interpretation of dose-dependent performance effects requires a recognition of the difference between CW dose levels necessitating medical treatment and levels yielding substandard performance. Although performance standards (return-to-duty indicators) are not defined for most drugs, a general case can be made that the dose level that produces substandard performance is at most equal to and often less than the level that requires medical treatment. For example, atropine sulfate may be given to treat the pulmonary effects of OP exposure, a medical emergency, but not necessarily to counteract miosis, a substandard-performance effect. This paper is based on sublethal dose-level effects on performance--levels at which the individual is expected to perform after treatment.

Where sufficient interval-level data exist, we will discuss performance effects in terms of the dose level (IM unless otherwise indicated) that produced any detectable performance change in a given percentage of the population studied. For example, ED50 will refer to the dose level at which the performance of 50% of the subjects is changed. The amount of change is, of course, another question. Where the data are insufficient for an interval-level analysis, such as in clinical observations and personal accounts, we will undertake a nominal or categorical analysis.

The profile of atropine sulfate symptomology, as extracted from the Pharmacological Basis of Therapeutics (16), Physician's Desk Reference (17), and AMA Drug Evaluations (1), can be interpreted at a nominal level, in the absence of interval-level data, to yield categories of aircrew performance decrement. Hypotensive effects can be expected to reduce alertness, and unusual visceral sensations such as tachycardia may stimulate anxiety. The inhibition of secretion from sweat glands will reduce heat tolerance and increase retention of toxic products, further reducing alertness. Loss of accommodation due to paralysis of ciliary muscles will reduce visual acuity--impairing map, dial, and radar-scope reading as well as hampering the operation of fire control, electronic countermeasures, bombardment/navigation, and flight control systems. Mydriasis due to inhibition of the sphincters of the iris will lead to photophobic response--e.g., avoidance of observing primary and secondary explosions--and flashblindness, as well as blurred vision that impairs writing and response-key selection. Atropine sulfate at low dosages will block central nervous system (CNS) inhibitory neurons, producing dizziness and vertigo that lead to lost equilibrium and 3-axis maintenance. High dosage will block CNS excitatory neurons, impairing memory and information processing and leading to reduced judgment and decision making as well as increased reaction time and loss of attention. Finally, decreased salivary secretion will peripherally impair speech.

The results of interval-level (metric) data may be extrapolated to the aircrew environment using the effective-dose (ED) percentile concept. This approach introduces the question of what percentage of drug effects constitutes a substandard condition in a sufficient number of airmen to warrant discontinuing the drug. The level of personal substandard physical or mental performance, based on a dose-response curve that relates the extent of performance lost to the dose amount in a single individual, is a medical and/or psychopharmacological issue. But the issue of what percentage of the

aircrew force may be put at risk in combat due to a drug effect is an operational rather than a medical question. For the purpose of analysis and interpretation we select, without recommendation, the ED5 level as an acceptable risk factor in aerial combat. Thus if an aircrew were taking a drug at the ED5 level, the commander would be risking 5% of his airborne force, due to expected performance decrement(s), if they went into aerial combat.

Effects on Vision, Thermoregulation, Coordination, Attention, and Memory

Headley's review (8) of the performance effects of unchallenged atropine sulfate is the most comprehensive synthesis of the issue yet published. His review, however, is oriented to Army field operations and not to aerial combat. For example, the interaction of atropine sulfate with altitude and G-forces is not considered. Headley identifies field-performance decrements in near-vision, thermoregulation, muscular strength/coordination, attention, and memory. Deficits in thermoregulation would be of less concern in an environmentally controlled cockpit than in a field environment, whereas muscular weakness would be of greater concern when operating under additional G-forces. Losses in memory, attention, and near-vision would appear even more critical when operating a supersonic aircraft than when engaged in field operations. Thus while the Headley review is the most comprehensive yet published, it has limited relevance to aerial combat, and in general the atropine data require reinterpretation for Air Force operations.

Based on a linear regression analysis of the near-vision data reviewed by Headley, the ED5 dose is 1.35 mg (see Figure 1). The function reaches a plateau between 2 and 3 mg and is exponential between 4 and 5 mg. Headley does not review visual performance effects below 2 mg. Bye et al. (2), however, report a change in visual near-point and resting-pupil diameter at .02 mg/kg (overall) in eight humans. This dose equates to approximately 1.4 mg/person oral and 0.7 mg/person IM, based on extrapolations suggested by Mirakhur's data (15). Mirakhur reports that pupillary dilation reaches statistical significance 5 h after IM injection with 0.5 or 1.0 mg. Thus the best available estimate of the ED5 level for visual near-point change is 1.35 mg; this is in agreement with the range of published results.

An interpretation of these results in terms of aircrew performance requires a distinction between combat and noncombat sorties. In Air Force noncombat sorties, any dose level of atropine would almost certainly lead to temporary grounding as suggested by the prohibition to fly after taking atropine expressed in U.S. Army Technical Manual 8-285. In combat operations, however, procedures change with contingencies. Although the ED5 level of 1.35 mg is an estimate, the ED40 level of 2 mg is based on actual data. At 32 mg, 40% of the aircrew force would be at risk as a result of change in near-vision point. The implication is that reading manuals, maps, radar scopes, and instruments as well as operating offensive/defensive fire control, navigation/bombardment, and flight director systems would be negatively affected.

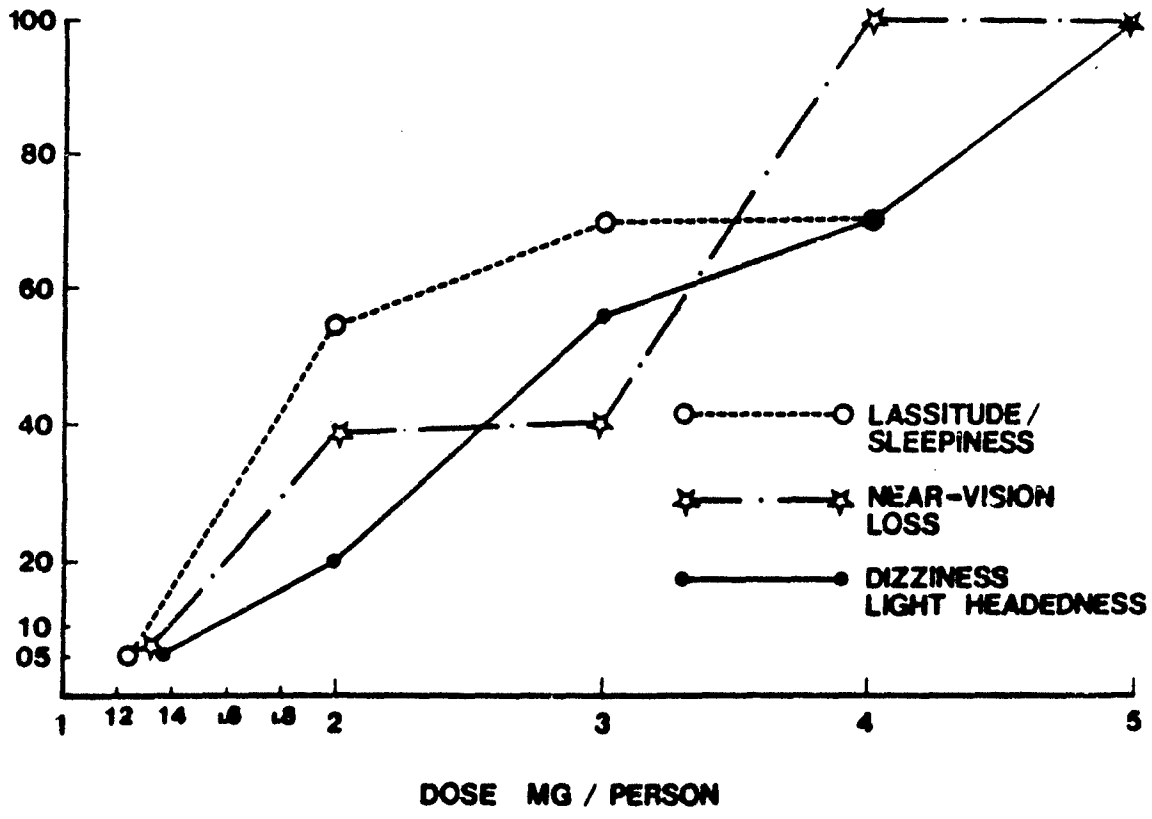

Figure 1. Extrapolated ED5 for subjective symptoms of atropine.

The extrapolated ED5 dose levels for lassitude/sleepiness (1.27 mg) and dizziness/light-headedness (1.33 mg) are also shown in Figure 1. Vertigo and the loss of alertness resulting from a dose range of 1.27 to 1.33 mg atropine would put 5% of the force at risk. The dose agreement of the ED5 extrapolations for vertigo, loss of alertness, and near-vision is of interest as it suggests a concurrence of action identifying a possible substandard performance level in general. (See also the next section, Effects on Saliva Dose-Response Curve.) Although these combined performance effects at the ED5 level may be related in a linear fashion to sortie loss rate during continuing combat operations, the effects may exponentially impact loss rate during the first ten sorties. During this period of skill development, the pilot's lack of combat experience puts him at high risk wherein a small decrease in performance can have a critical effect.

Effects on Saliva Dose-Response Curve (DRC)

Lonnerholm and Widerlov (12) measured the percentage of saliva lost after 0.25, 0.40, 0.75, and 1.5 mg atropine sulfate IV. Since the mode of the administration (IM vs. IV) affects only the rate of absorption and not the magnitude of effect, these data can be related to maximal effects IM. Figure 2 shows an idealized atropine-saliva DRC base on a linear regression equation using Lonnerholm and Widerlov's data (12). The percentage of remaining saliva at 2 mg is minimal, and no additional performance effect would be expected beyond that level.

In terms of aircrew performance the atropine saliva data may be interpreted to indicate an impairment of speech, particularly enunciation. Cullumbine et al. (4) report difficulty in giving orders, but a speech capacity does remain beyond the 2-mg point. An atropine speech-loss DRC has not been reported, and such research is needed. In terms of aircrew performance, altitude effects probably would not interact with this mode of atropine action; however, dehydration and excitement would. In aerial combat emotional excitement would suppress salivation in a situation often requiring rapid speech, as in giving surface-to-air missile warnings.

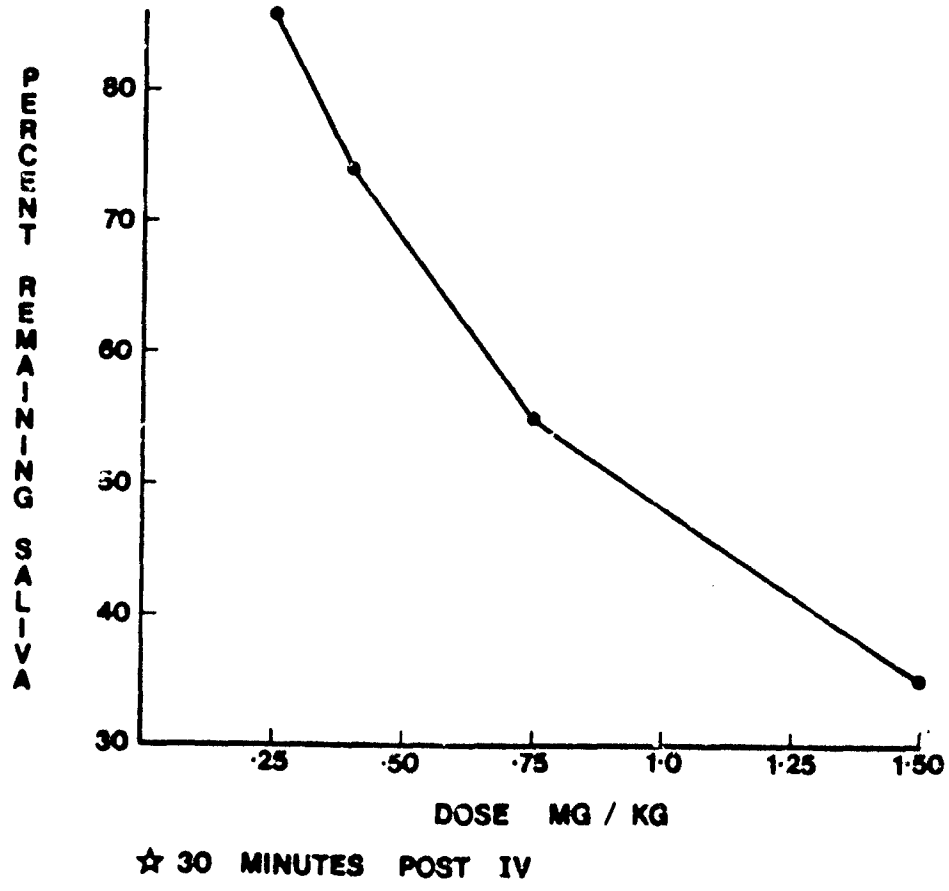

Figure 2. Atropine - Saliva DRC in humans.

Effects on Sleep

Atropine significantly increases the duration of slow wave sleep (SWS) per hour in rats (23). The atropine-SWS DRC shown in Figure 3 is extracted from Santucci et al. (23) and extrapolated for intervening values. At 10 mg/kg and above, the increased duration in SWS is statistically significant. Conversely, Usui and Iwahara (25) report that atropine delays REM onset and decreases REM episode duration in rats. Comparable DRC data in humans is not available; however, Toyoda et al. (24) report similar effects in humans (only the abstract is available). In terms of aircrew performance, atropine could exacerbate sleep-cycle problems due to time-zone changes, yielding all of the performance effects, especially decreased alertness, that accrue to sleep-cycle changes. The interaction of atropine with shifts in sleep cycles has not been tested.

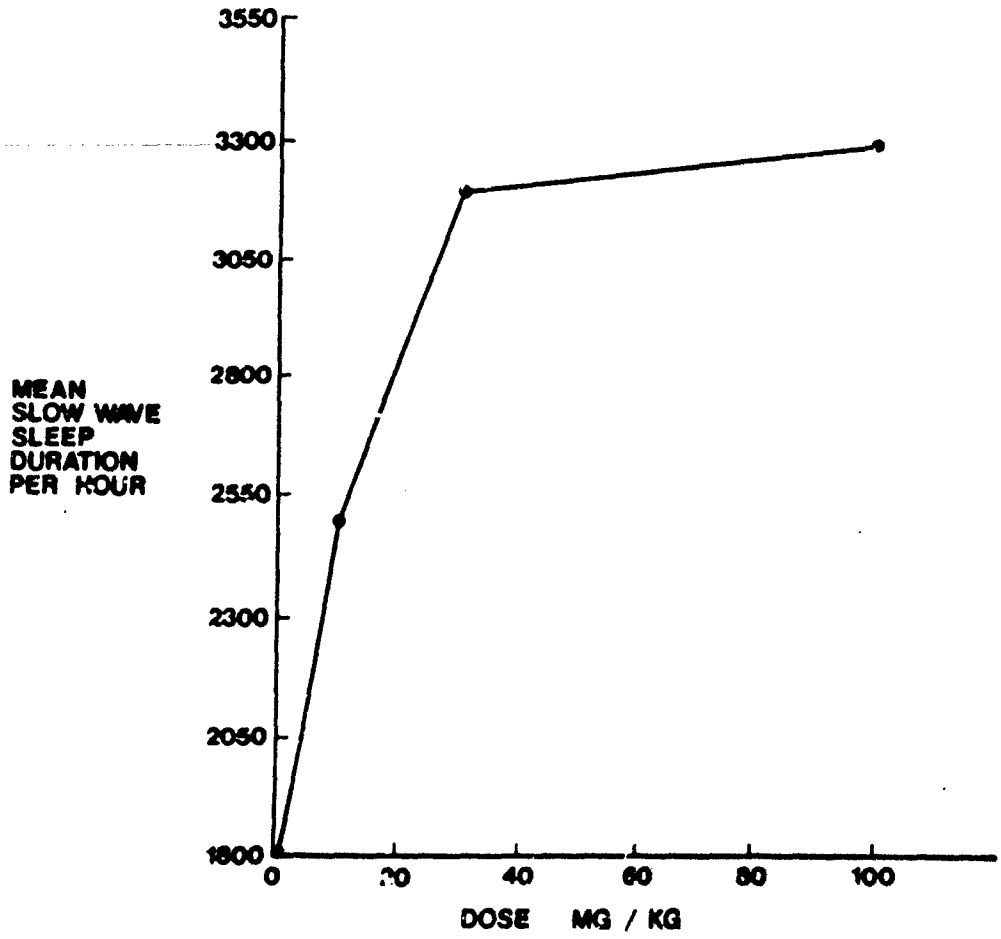

Figure 3. Atropine - Slow wave sleep DRC in rats.

Effects on Response-Force Accuracy DRC

Atropine effects on response-force measures are not reported in humans; however, Preston and Schuster (18) measured accuracy of response-force discrimination as a function of 0.1, 0.2, and 0.4 mg/kg IM atropine sulfate. Three rhesus monkeys were required to press a lever with at least 25 but less than 40 g of force for 3 s. The DRC for this task is shown in Figure 4, in which the 0.3 mg/kg data point is an extrapolation. This curve shows a significant decline in response-force accuracy beyond 0.2 mg/kg; this corresponds to 0.03 mg/monkey or 0.025 mg/man when the Mattsson et al. (13) equipotent extrapolation equations are applied. Regardless of the validity of these extrapolations, response-force accuracy is dose dependent and fine motor discriminations in man would be impaired with 2 mg atropine sulfate.

Decreased response-force accuracy would be critical in manual operation of flight controls and dial adjustments such as radiofrequency fine-tuning. In multiengine aircraft in which the advancing and retarding of throttles must be nearly coincident, a loss of fine motor discrimination would appear particularly critical.

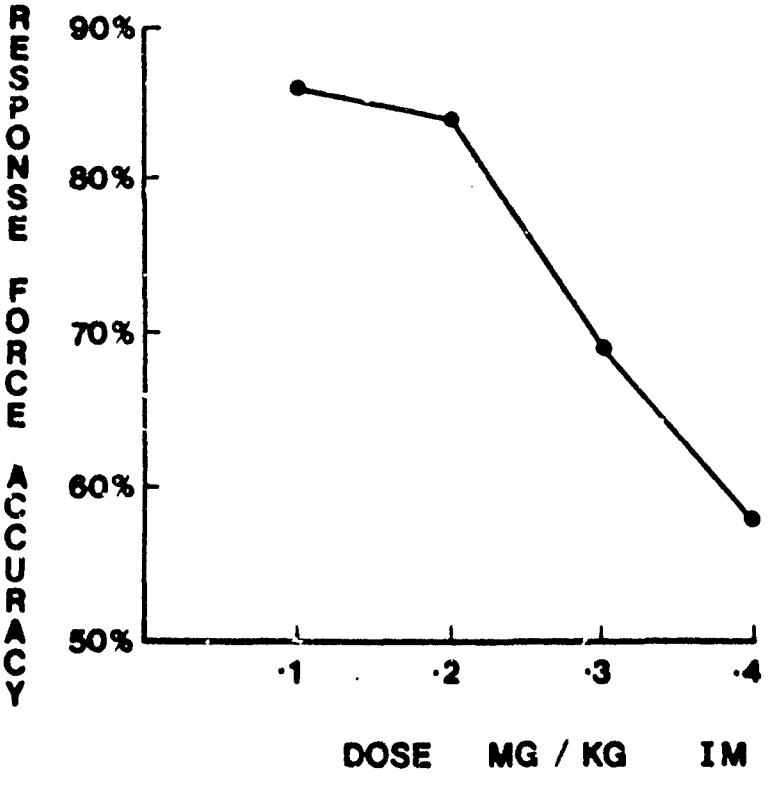

Figure 4. Atropine - Response-force accuracy DRC in Monkeys.

Effects on Performance-Rate DRC

Chait and Balster (3) examined variable-interval (VI) 100-s performance as a function of 0.05 to 3.2 mg/kg atropine sulfate in three squirrel monkeys. (See Figure 5.) A significant decrease in performance is seen between 0.05 and 0.10 mg/kg; and if the equipotent extrapolation equation (13) were applied, a similar result would be expected in humans at 0.037 to 0.06 mg/kg (2.9 to 4.8 mg/person). Variable-interval-schedule performance is a complex behavior with no specific implications for aircrew performance. The best interpretation appears to be one either of overall performance or the rate of performance on any given task.

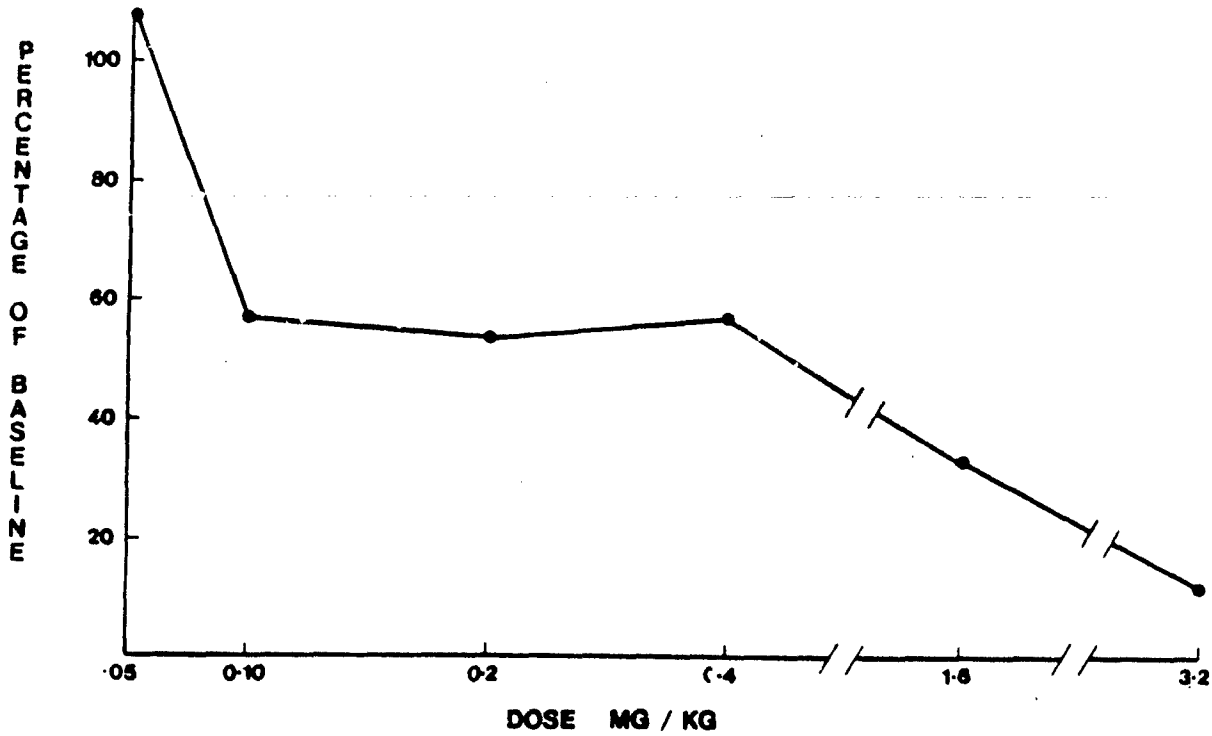

Figure 5. Atropine - Variable-interval 100-s performance in monkeys.

VISUAL EFFECTS OF AN ATROPINE SULFATE CHALLENGE TO AN ANTICHOLINESTERASE

The visual effects in humans of an atropine sulfate challenge to a cholinesterase inhibitor are not reported. Revzin (20) took single-unit recordings from rostral projections of the superior colliculus in pigeons injected with atropine sulfate and an organophosphate (Mevinphos). The single units from which Revzin recorded were sensitized to direction and velocity of an object moving in a field. Both atropine and Mevinphos abolished directional specificity of these single units, with the implication that atropine does not counteract the visual-field performance decrement of an anticholinesterase.

Although the visual systems of the Aves may offer generalizations to humans, the mode of atropine metabolism is significantly different in humans; this difference reduces the extent to which Revzin's results (20) can be interpreted for aircrew. Revzin (21), however, observed visual effects in three squirrel monkeys injected with an LD10 dose of Mevinphos (0.4 mg/kg). When symptoms of OP poisoning were seen, the squirrel monkeys were treated with 2 mg/kg atropine sulfate every 3 min until the parasympathomimetic signs of OP poisoning disappeared. The total treatment dosages for the three monkeys were 30 mg/kg, 15 mg/kg, and 6 mg/kg. All subjects recovered; however, for the first 1.5 h following the titration procedure, the monkeys were blind—neither responsive to objects moving in a visual field nor to direct light sources directed in the eyes.

The dosages which Revzin (21) reports are well below those reported in the treatment of OP poisoning in man (7), although they exceed the atropine field-kit levels. Whether or not the coincident effects of blockers and inhibitors occur at the 2- to 6-mg total dose level is an untested but needed research question. Revzin's work (20, 21) is also significant in that it extends the visual performance decrement effects from peripheral to central modes of action. At the most conservative level of interpretation, the use of atropine sulfate to neutralize the central visual effects of anticholinesterases in aircrew is questionable.

DRUG INTERACTIONS

Three categories of drugs allowed by Air Force Regulation 160-12 for use while engaged in duties involving flying have potentially adverse effects when taken concurrently with atropine. Epinephrine may be waived when used topically for glaucoma, but a pilot with glaucoma would experience increased interocular pressure accompanied by eye pain. The drug interaction may exaggerate dilation of the pupil and enhance photophobic response. The concurrent use of antihypertensives such as chlorothiazide, hydrochlorothiazide, or triamterene may result in excessive hypotension effect. Finally the concurrent use of probenecid or allopurinal for gout or hyperuricemia may inhibit the bladder, increase dysuria with pain, and reduce urinary frequency contrary to the purpose of probenecid.

CONCLUSIONS

Although atropine may be appropriate for treating medical emergencies, especially pulmonary effects, it is apparently not appropriate for counteracting performance effects of acetylcholinesterase inhibitors. The high degree of atropine tolerance in cases of OP poisoning—as well as common modes of action, especially visual, between the agonist and antagonist—argue against choosing atropine sulfate to manage CW antiperformance effects on aircrew. Actual experiments with humans have not and probably will not be conducted; however, animal data and medical OP-poisoning histories are sufficient to warrant a conclusion that if the experiments were done. the results would be negative.

In the case of atropine sulfate, several dose-response curves have been published and the state of knowledge appears sufficient to warrant the conclusion that 2 mg atropine would put 40% of an aircrew force at risk due to loss of near-vision, alertness, equilibrium, response-force discrimination, and enunciation. Information processing may also be affected. Prolonged use may interfere with sleep-cycle adjustments. These negative effects may appear in 5% of the aircrew force at the 1.35-mg/person level; however, the potential beneficial contribution to combat effectiveness in an exposed aircrew force cannot be excluded, particularly when atropine is used in a combination drug. Without human experiments, a final conclusion awaits testing under real-life conditions. The fundamental dilemma is that any antidote will itself have negative effects, thus raising the basic question: can any pharmacological solution to chemical warfare exist for a high-technology battlefield.

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